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PRD2009-12

Proposed Registration Decision

Diallyl Disulfide and Related Sulfides

(publié aussi en français)

17 September 2009

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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Canada

HC Pub: 8354

ISBN: 978-1-100-13311-9 (978-1-100-13312-6)
Catalogue number: H113-9/2009-12E (H113-9/2009-12E-PDF)

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Overview

Proposed Registration Decision for Diallyl Disulfide and Related Sulfides

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of DADS Technical and DADS, a fungicide containing diallyl disulfide and related sulfides, which suppresses white rot (*Sclerotium cepivorum)* disease on onion and other bulb vegetables.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of DADS Technical and DADS.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on diallyl disulfide and related sulfides, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on diallyl disulfide and related sulfides, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Diallyl Disulfide and Related Sulfides?

Diallyl disulphide and related sulfides are the active ingredients in the end-use product DADS fungicide, which is based on a natural metabolite of garlic. DADS fungicide suppresses white rot (*Sclerotium cepivorum* Berk.) disease on onion and other bulb vegetables, by reducing the level of *Sclerotium cepivorum* inoculum in the soil in the absence of a host crop.

Health Considerations

Can Approved Use of Diallyl Disulfide and Related Sulfides Affect Human Health?

Diallyl disulfide and related sulfides are unlikely to affect human health when used according to label directions.

Exposure to diallyl disulfide and related sulfides may occur when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

The technical grade active ingredient, diallyl disulfide and related sulfides, is highly acutely toxic by the oral route, slightly acutely toxic by the dermal route, minimally irritating to eyes, severely irritating to skin, a skin sensitizer, not a mutagen, and a respiratory irritant.

Due to the toxic and irritative potential of diallyl disulfide and related sulfides, the principal display panels of the DADS Technical and DADS end-use product labels are required to state: "DANGER (PICTOGRAM) POISON", "DANGER -

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

SKIN IRRITANT", "POTENTIAL SKIN SENSITIZER", and "Contains garlic allergen." In addition, the principal display panels of the technical and end-use product labels are required to have the statements: "Prevent access by unauthorized personnel" and "Keep out of reach of children and prevent access by unauthorized personnel" respectively. The "PRECAUTIONS" section on the secondary display panels of both the labels are required to include: "DO NOT use if allergic to garlic. Fatal or poisonous if swallowed. May be harmful if absorbed through the skin. Harmful if inhaled. Avoid inhaling/breathing vapours or fumes. May irritate eyes. Avoid contact with eyes. Severely irritating to the skin. DO NOT get on skin. Potential skin sensitizer. Avoid contact with clothing." These cautionary statements are considered to be sufficient to minimize any human health and safety concerns.

Waivers were granted for short-term toxicity, reproduction and developmental toxicity, and genotoxicity studies based on the end-use product proposed use pattern, method of application and the anticipated low potential for exposure when applied as directed.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Diallyl disulfide and related sulfides are not applied directly to food or feed crops. Dietary risk to humans is considered negligible based on the intended use, method of application, and low application rate.

Diallyl disulfide and related sulfides are non-persistent in the environment (half life < 4 hours in water/soil); therefore, crops planted three months after the application of diallyl disulfide and related sulfides are unlikely to result in food residues.

Occupational Risks From Handling Diallyl Disulfide and Related Sulfides

Occupational risks are not of concern when diallyl disulfide and related sulfides are used according to label directions, which include protective measures.

Occupational exposure to diallyl disulfide and related sulfides is expected to be negligible as the proposed method of application is by direct injection into the soil column at a low application rate (2%), and the treated soil is to be packed immediately with a mechanical packer.

Precautionary statements on the label (for example, wearing of personal protective equipment) are considered adequate to protect individuals from any unnecessary risk due to occupational exposure.

Environmental Considerations

What Happens When Diallyl Sulfides and Related Sulfides are Introduced into the Environment?

Diallyl disulfide and related sulfides are naturally occurring compounds found in *Allium* crops. From the proposed use pattern, negligible diallyl disulfide and related sulfides will enter the environment as compared to agricultural sources such as fields planted with garlic and onions.

Diallyl disulfide and related sulfides are soluble in water and have low mobility in soil. Due to their high volatility, diallyl disulfide and related sulfides are non-persistent in terrestrial and aquatic environments. Diallyl disulfide and related sulfides are expected to volatilize from dry, wet or moist surfaces; the vapor-phase diallyl disulfides are expected to be readily degraded in the atmosphere by reactions with photochemically produced hydroxyl radicals.

Diallyl disulfide and related sulfides are expected to pose negligible risk to terrestrial and aquatic organisms under conditions of use.

Value Considerations

What Is the Value of DADS fungicide?

There is currently only one other product available to growers for the management of white rot disease on garlic and onions. The registration of DADS fungicide will provide growers with another alternative. In addition, diallyl disulfide and related sulfides represent a new mode of action for the suppression of the disease, which is unlikely to lead to resistance development in the pathogen population, based on the mode of action and method of use.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of DADS to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

In order to mitigate the inappropriate use of the product and help avoid accidental exposure, the principal display panels of the DADS Technical and end-use product labels are required to have the statements, "Prevent access by unauthorized personnel" and "Keep out of reach of children and prevent access by unauthorized personnel", respectively.

Because there is a concern for potential inhalation exposure during loading or when handling the concentrated end-use product (90% w/w, active ingredient), workers must use a NIOSH/MSHA approved supplied-air respirator during those activities.

The personal protective equipment proposed on the end-use product label includes the NIOSH/MSHA approved supplied-air respirator during clean-up in case of spill or leak and during clean-up and repair activities, chemical goggles for eye protection and the wearing of rubber or neoprene gloves and a protective garment to prevent skin contact. The label also states that the product is not to be applied to the soil surface, the treated surface area is to be sealed using a mechanical packer immediately after application, and the treated soil is not to be disturbed for 90 days after sealing.

Environment

Risk to non-target organisms will be mitigated by appropriate label precautions.

What Additional Scientific Information is Being Requested?

Chemistry

The following studies are required, as a condition of full registration, to complete the chemistry database for this product:

- Storage stability data for DADS, the end-use product, representing at least one year of storage at ambient conditions. This is expected to be complete during 2010.

Next Steps

Before making a final registration decision on diallyl disulfide and related sulfides, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications. The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on diallyl disulfide and related sulfides (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Diallyl Disulfide and Related Sulfides

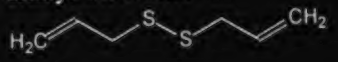
1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	diallyl disulfide and related sulfides	
Function	fungicide	
Chemical name		
1. **International Union of Pure and Applied Chemistry (IUPAC)**	diallyl disulfide *OR* 3,3′-disulfanediylbis(prop-1-ene) diallyl sulfide *OR* 3,3′-sulfanediylbis(prop-1-ene) diallyltrisulfane diallyltetrasulfane	
2. **Chemical Abstracts Service (CAS)**	disulfide, di-2-propen-1-yl 1-propene, 3,3′-thiobis trisulfide, di-2-propen-1-yl tetrasulfide, di-2-propen-1-yl	
CAS number	diallyl disulfide: diallyl monosulfide: diallyl trisulfide: diallyl tetrasulfide:	2179-57-9 592-88-1 2050-87-5 2444-49-7
Molecular formula	diallyl disulfide: diallyl monosulfide: diallyl trisulfide: diallyl tetrasulfide:	$C_6H_{10}S_2$ $C_6H_{10}S$ $C_6H_{10}S_3$ $C_6H_{10}S_4$
Molecular weight	diallyl disulfide: diallyl monosulfide: diallyl trisulfide: diallyl tetrasulfide:	146.28 114.21 178.34 210.41

Structural formula

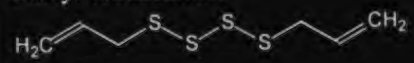
diallyl disulfide:



diallyl monosulfide:

diallyl trisulfide:

diallyl tetrasulfide:



Purity of the active ingredient 100% nominal

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—DADS Technical

Property	Result
Colour and physical state	Light yellow to orange liquid
Odour	Pungent garlic
Melting range	Not applicable
Boiling point or range	176°C
Density at 25°C	1.03
Vapour pressure at 20°C	1.2 kPa
Henry's law constant at 25°C	3.8×10^{-2} atm m^3/mole
Ultraviolet (UV)-visible spectrum	Not expected to absorb at λ>200 nm
Solubility in water at 25°C	0.006%
Solubility in organic solvents at 25°C	**Solvent** — **Solubility (%)** isooctane — 1.86 2-propanol — 7.01 acetone — 100
n-Octanol-water partition coefficient (K_{ow})	Estimated at 3.56
Dissociation constant (p*Ka*)	Does not dissociate
Stability (temperature, metal)	Exposure to heat or ferric chloride converts the diallyl disulfide to the mono-, tri- and tetrasulfides. Stable to sunlight and to other metals.

End-Use Product—DADS

Property	Result
Colour	Yellow-brown
Odour	Strong garlic/onion
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Guarantee	90% nominal
Container material and description	Unlined steel pails or Level D fluorinated high-density polyethylene (HDPE) drums and totes, 115 to 1025 L
Specific gravity at 25°C	1.02
pH	6.0 for a 5% emulsion
Oxidizing or reducing action	Reacts with oxidizing and reducing agents; strong alkali should also be avoided
Storage stability	Not yet provided
Corrosion characteristics	Not corrosive to carbon or stainless steel or fluorinated HDPE over 12 months
Explodability	Not expected to be explosive

1.3 Directions for Use

DADS fungicide will suppress white rot on bulb vegetables. It is injected into the soil at least six months before planting at the rate of 10 L of fungicide in a minimum of 500 L water per hectare. Fields should be seed-bed ready prior to application. Apply the product when the average soil temperature (24 h period) at 10 cm depth is 20°C and falling (fall season) or 9°C and rising (spring). Soil moisture must be 50–70% field capacity. No *Allium* spp. plants are to be present in the field for a period of six months after treatment. Inject material into the soil and cover soil. Do not apply to the surface of the soil.

1.4 Mode of Action

DADS has a unique mode of action. The active ingredient is a metabolite of *Allium* spp. It acts as a fungal attractant to stimulate germination of the sclerotia of the disease pathogen, *Sclerotium cepivorum*. When applied to the field six months before the host crop is to be planted, the pathogen germinates, and without a host to further complete its life cycle, it either dies or forms new but weakened sclerotia.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The method provided for the analysis of the active ingredients in DADS Technical has been validated and assessed to be acceptable for the determination.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

Methods for residue analysis were not required.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for diallyl disulfide was conducted. The database is considered adequate, consisting of Tier I toxicity studies and waiver rationales. The scientific quality of the data is acceptable and the database is considered adequate to define the majority of the toxic effects that may result from exposure from the intended use of this chemical pest control product.

The applicant submitted acute toxicity, irritation, sensitization, and genotoxicity studies, and data waiver requests to meet the toxicological evaluation requirements for both the technical grade active ingredient and end-use product. All the submitted studies were conducted with the active ingredient, diallyl disulfide. Although the PMRA requires toxicity and irritation studies to be conducted with both the technical grade active ingredient and the end-use product, given that the end-use product contains no formulants of toxicological concern, testing with the active ingredient was considered acceptable.

Diallyl disulfide was highly acutely toxic by the oral route and slightly acutely toxic by the dermal route. A request to waive acute inhalation toxicity testing was submitted which was acceptable on the basis of negligible risk from the method of application, mitigative statements and personal protective equipment requirements on the label. Diallyl disulfide was minimally irritating to the eyes and severely irritating to the skin in New Zealand white rabbits. Diallyl disulfide is a dermal sensitizer. The genotoxicity of diallyl disulfide was assessed with the reverse gene mutation assay in bacteria (Ames assay) and found to be negative. Waivers were granted for short-term toxicity, reproduction and developmental toxicity, and further genotoxicity studies because humans are exposed to diallyl sulfides from the consumption of Allium crops. Allium crops, including garlic, have a long history of use in the human diet, so it is very unlikely

that diallyl disulfide and its related sulfides will have significant adverse effects in humans from the anticipated low level of exposure from the proposed use pattern.

In the published scientific literature, acute effects of diallyl disulfide in humans have been reported from an incident of a chemical release from a damaged package in air cargo. Large numbers of workers exposed to the chemical fumes showed acute toxic symptoms consisting of nausea, vomiting, throat irritation, irritation of eyes, lacrimation, itching and rhinorrhea. The chemical fumes had the characteristic odour of sulfur, and were identified by gas chromatography-mass spectrometry (GC-MS) as diallyl disulfide, originating from garlic oil, which was released from a leaking container. This indicates the severity and acute human adverse effects from inhalation exposure to concentrated garlic oil which has diallyl disulfide as the major ingredient.

3.2 Determination of Acute Reference Dose

As DADS fungicide is not intended for direct application to food crops, an acute reference dose is not required.

3.3 Determination of Acceptable Daily Intake

As DADS fungicide is not intended for direct application to food crops, an acceptable daily intake is not required.

3.4 Food Residue Exposure Assessment

A request to waive the requirement for plant metabolism and food residue was submitted based on the following considerations:

1) DADS fungicide will be injected directly into the soil at a low use rate, in the absence of a crop; therefore, there is no assimilation and metabolism of the active by the plants to result in plant residues;

2) diallyl sulfides are volatile compounds and tend to move readily through dry soils, limiting accumulation for availability to subsequent crops;

3) DADS fungicide is not applied directly to any crop that will be fed to humans or livestock;

4) diallyl sulfides are naturally occurring compounds found in Allium crops, including onion and garlic, which helps to repel most non-target organisms, and

5) the rapid breakdown and volatility of the active ingredient results in non-persistence in the environment which will reduce the potential for exposure from food.

Due to the proposed use pattern, the method of application and the anticipated non-persistence of diallyl disulfide and its related sulfides in the soil, the application of DADS is unlikely to result in significant food and feed residue exposure; therefore, the waiver request is acceptable. Moreover, humans are exposed primarily to diallyl disulfide and its related sulfides directly from food when they consume garlic, onions, leeks and other Allium crops, and there have been no reported adverse health effects of concern from the food use of these crops. No Codex maximum residue limits (MRLs) are set for the residues of diallyl sulfides in or any food or feed crop. Since diallyl disulfide is applied to bare soil three months prior to planting, and is non-persistent in the environment (half-life in soil < 4 hours), the promulgation of a maximum residue limit for diallyl disulfide was not considered necessary for this use pattern.

3.5 Occupational and Bystander Risk Assessment

3.5.1 Toxicological Endpoints

Occupational exposure to DADS is expected to be short term and predominantly by the inhalation route. Dermal exposure and oral exposure are also possible by improper handling or from failing to observe the label directions. There is a potential for inhalation exposure while handling the concentrated end-use product, and also during spills, leaks or clean-up activities. Although a margin of exposure could not be estimated with available information, it is not expected that exposure to DADS, when label instructions and precautions are observed, will result in any significant potential for adverse effects.

3.5.2 Use Description /Exposure Scenario

DADS is to be injected into the soil using 30-cm injection shanks, and the depth of injection will depend on how deep the field is cultivated. The distance between two shanks has been proposed at 20 cm, and the injection outlet ports are to be positioned at 7.5, 15, 23 and 30-cm depths. Treatment of the whole tilled soil profile is recommended, and the product is not to be applied to the soil surface. The proposed rate of application is 10 L of DADS in a minimum of 500 L of water per hectare. During the fall and spring seasons, DADS is to be applied when the average temperature in a day at 10 cm soil depth is 20°C or below and 9°C or above, respectively, and the recommended soil moisture is 50 to 70 % of the field capacity.

In a typical eight-hour work day, a crew could treat up to a maximum of 50 hectares of agricultural field, but the typical range is likely to be 30 to 50 hectares. According to the data submitted, the range of active ingredient (diallyl disulfide) handled would be 275 kg (30 ha × 10 L/ha × 90% active ingredient × 1.02 kg/L) to 459 kg (50 ha × 10 L/ha × 90% active ingredient × 1.02 kg/L). One worker would typically handle a maximum of 450 L of active ingredient in one work day (50 ha × 10 L/ha application rate × 90% active ingredient).

3.5.3 Mixer, Loader and Applicator Exposure and Risk Assessment

No mixing is required, so there is no occupational risk to mixers.

Inhalation exposure during loading is of concern if loaders are not protected from volatile vapour/fumes. Due to the volatility of the technical grade active ingredient, adverse health effects are likely to occur from inhalation. In the published literature, there have been reports of occupational asthma or rhinitis caused by occupational exposure to garlic dust in adults and children helping their parents with the harvesting of garlic. Garlic dust is capable of inducing an immediate-type allergic reaction when inhaled.

Diallyl disulfide is the primary allergen of garlic and the main component of garlic oil. Because of diallyl disulfide's volatile nature, inhalation exposure to DADS is very likely to induce adverse effects in humans. Diallyl disulfide is reported as being irritating to the respiratory tract.

Although the low use rate, application by a direct mechanical closed shanking system, and use of a mechanical packer following soil treatment minimizes inhalation exposure for applicators, inhalation exposure during loading or while handling the concentrated end-use product (90% w/w active ingredient) is not adequately mitigated. Moreover, the product is packaged in 1–210 L plastic drums, and will be poured into the application equipment. Drums can be cumbersome to manage when loading a volatile fluid, and spill or leakage may be possible for which clean up is required.

Based on the volatility of DADS and the acute toxicological concerns associated with diallyl disulfide, the mitigative statement "Avoid breathing vapours / fumes" is required on the label in addition to the wearing of a NIOSH/MSHA approved supplied-air respirator during handling of the concentrated product at loading as well as during spill and leakage already proposed on the draft label.

Additional personal protective equipment includes chemical goggles for eye protection, and rubber or neoprene gloves and protective garments to prevent skin contact. The label also states that the product is not to be applied to the soil surface, the treated surface area is to be sealed using a mechanical packer immediately after application, and the treated soil is not to be disturbed for 90 days after sealing.

3.5.4 Bystander Exposure and Risk Assessment

Bystander exposure is anticipated to be negligible because the commercial application of DADS is expected to involve authorized personnel only, and the proposed method of application involves direct soil injection using a mechanical closed shanking system.

3.5.5 Postapplication Exposure

Postapplication activity involves mechanical packing of the soil immediately after application of the end-use product. Since DADS application is not on the soil surface, but via injection into the soil column, minimal occupational exposure is expected from postapplication mechanical packing. Furthermore, postapplication exposure is limited by restriction of activities on the treated sealed soil for 90 days. Due to the rapid environmental degradation (half life < 4 hours in soil) and volatile nature of DADS, activities after the 90-day post-treatment period are unlikely to result in occupational risk.

The recommended personal protective equipment (PPE) and additional statements of mitigation, precaution and hygiene already present on the product label are adequate to protect workers from exposure, assuming all label directions are observed.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Diallyl disulfides are soluble in water and will not bioaccumulate. The vapour pressure (12 mmHg) and Henry's law constant (3.8×10^{-2} atm m^3/mole) of the main active component, suggest that diallyl disulfide would be highly volatile from water surface and dry or moist soil. The vapour-phase is expected to be rapidly transformed in the atmosphere by reactions with photochemically produced hydroxyl radicals. A long-range transport is not expected. Diallyl disulfides have low potential to leach to groundwater.

Data on the fate and behaviour of diallyl disulfide are summarized in Appendix I, Table 2.

4.2 Effects on Non-Target Species

No data were submitted by the registrant addressing potential toxic effects of diallyl disulfide to non-target species. Since diallyl disulfide acts as a nonselective soil fumigant some terrestrial organisms are expected to be targeted by diallyl disulfide. However, because of the high volatility of diallyl disulfide, the proposed use pattern will result in minimal exposure to terrestrial organisms and negligible risk is expected.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

Bulb Vegetables (Allium spp.)

Five onion trials (four field and one greenhouse) from Ontario (1995 to 2000) were evaluated. The results of the five trials indicate that diallyl disulfide, when applied at 10 L/ha, stimulates the germination of sclerotia of *Sclerotium cepivorum*. Under conditions of low disease pressure, germination in the absence of a host (for example, *Allium* spp.) reduces the pathogenicity of the disease organism (33 to 100% control) in the subsequent year.

5.2 Phytoxicity to Host Plants

Phytotoxicity was not reported in any of the onion trials.

5.3 Impact on Succeeding Crops

It is important that no *Allium* spp. crops be planted in the treated soil until at least six months after application since *Sclerotium cepivorum* will be active during this time.

5.4 Economics

There are approximately 6000 hectares of onions grown in Canada and approximately one third of the area is infected with the pathogen. Onions cannot be grown in some areas because the disease pressure is too high.

5.5 Sustainability

5.5.1 Survey of Alternatives

There is only one product currently registered for use on white rot of onion, Botran 75W Fungicide (Registration Number 8772, active ingredient dichloran).

5.5.2 Compatibility with Current Management Practices

This product should complement current management practices based on the unique mode of action.

5.5.3 Resistance Management

DADS fungicide is the only product with the active ingredients diallyl disulphide and related sulfides. There are neither reports of resistance, nor of cross-resistance with other fungicide groups.

5.5.4 Contribution to Risk Reduction and Sustainability

The active ingredient in DADS fungicide is based on a naturally occurring compound produced by garlic plants. Its ability to stimulate the germination of sclerotia of *Sclerotium cepivorum* is a unique method of suppressing disease in bulb vegetable crops and is a useful alternative to Botran 75W Fungicide.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances (those that meet all four criteria outlined in the policy, i.e. CEPA-toxic or equivalent, predominantly anthropogenic, persistent and bio-accumulative).

During the review process, diallyl disulfide (a major active component of diallyl disulfide and related sulfides, DADS technical) was assessed in accordance with Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy* and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Diallyl disulfide does not meet the Track 1 criteria and is not expected to form any transformation products which meet the Track 1 criteria. Diallyl disulfide is a naturally occurring substance and is not expected to be persistent or bioaccumulative in the environment.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette.*[5] The list is used as described in Notice of Intent NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act* and is based on existing policies and regulations including Regulatory Directive DIR99-03 and Regulatory Directive DIR2006-02, *Formulants Policy and Implementation Guidance Document*, and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade diallyl disulfide and related sulfides and the end-use product DADS fungicide do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The available information for diallyl disulfide and related sulfides is adequate to qualitatively identify the toxicological hazards that may result from human exposure to these chemicals. Submitted information suggests that diallyl disulfide is highly acutely toxic by the oral route, slightly acutely toxic by the dermal route, minimally irritating to eyes, severely irritating to skin, a skin sensitizer, not a mutagen, and a respiratory irritant.

Occupational exposure to diallyl disulfide and related sulfides is expected to be minimal from the proposed use pattern if the recommended PPE on the product label, which are intended to minimize worker exposure, are observed. Bystander exposure is also expected to be negligible.

Dietary exposure to diallyl disulfide and related sulfides from the application of DADS is expected to be negligible to non-existent.

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[5] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7.2 Environmental Risk

Based on the use pattern for DADS fungicide which includes direct injection into soil using enclosed shanking system, DADS presents a negligible risk to non-target terrestrial and aquatic organisms.

7.3 Value

The information and data reviewed for DADS fungicide are adequate to support a claim of suppression of white rot (*Sclerotium cepivorum)* disease on onion and other bulb vegetables, when applied at a rate of 10 L product/ha.

8.0 Proposed Regulatory Decision

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of DADS Technical and DADS, containing diallyl disulfide and related sulfides, which suppresses white rot (*Sclerotium cepivorum)* disease on onion and other bulb vegetables.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

°C	degree centigrade
µg	micrograms
a.i.	active ingredient
atm	atmosphere
BAF	bioaccumulation factor
BCF	bioconcentration factor
bw	body weight
CAS	Chemical Abstracts Service
CEPA	Canadian Environmental Protection Act
cm	centimetres
DACO	data code
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in the test population)
GC-MS	gas chromatography-mass spectrometry
h	hour(s)
ha	hectare(s)
HDPE	high-density polyethylene
Hg	mercury
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
kPa	kilopascal(s)
L	litre
LOQ	limit of quantitation
m	metre(s)
mg	milligram
mL	millilitre
mm	millimetre(s)
MAS	maximum average score
MIS	maximum irritation score
MRL	maximum residue limit
nm	nanometres
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PPE	personal protective equipment
ppm	parts per million
TSMP	Toxic Substances Management Policy

Appendix I Tables and Figures

Table 1 Acute Toxicity of Diallyl Disulfide and Its Associated End-Use Product (DADS)

Study	Species/Strain and Doses	Results	Target Organ/Significant Effects/ Comments
Oral Gavage 14-day study	Rat – Sprague-Dawley Dose: A single oral dose of diallyl disulfide at doses of 200, 600, 1000 (5/sex) or 5000 (10/sex) mg/kg bw (purity not known)	LD_{50} (mg/kg bw) ♂: 346 ♀: 346 ♂♀: 346	100% mortality in high dose group (600, 1000 and 5000 mg/kg/bw) Salivation, breathing abnormalities, decreased activity, wobbly gait, and pilo-erection were seen in treated animals. Hemolytic anemia; also observed in rodents fed diets rich in sulfur derived from onion and garlic. **High acutely toxic**
Dermal toxicity 24-hour exposure 14-day study	Rabbit–New Zealand white (5/sex/dose group) (purity not known) Single topical application of dially disulfide at doses of 1500, 1750, or 2000 mg/kg bw	LD_{50} (mg/kg bw) ♂: 1826 ♀: 2009 ♂♀: 1967	Notable clinical abnormalities include wobbling of animal's head when trying to move, decreased activity, wobbly gait, decreased defecation, diarrhea/soft stools, tremors, reddish colored urine, eyelids partially closed, lacrimation, white nasal discharge, eyes appear pale in color, breathing abnormalities, dilated pupils, apparent paralysis of hind limbs, hyperextension of limbs, and dermal irritation at the site of application. **Slightly acutely toxic**
Inhalation	Data Waiver Request: Rationale: DADS will be injected into the soil using a mechanical closed injection system, thereby eliminating the potential for inhalation exposure. The product label states " Do not apply to soil surface" and "contains allergen garlic". Applicant did not address occupational exposure during loading. The precautionary statement "avoid breathing vapours/ fumes" is not sufficient, due to the volatility of the product. Use of respirator is recommended when loading and handling concentrated end-use product (90%). Acceptable with PPE recommendations on label (above).		

Study	Species/Strain and Doses	Results	Target Organ/Significant Effects/ Comments
Primary Eye Irritation 24-hour exposure 7-day study Irritation scored by the method of Draize	Rabbit - New Zealand White (1 ♂, 5 ♀) Dose: 0.1 mL (purity not known). After 24-hour exposure, any residual test material in the eyes was removed by washing.	Maximum average score (MAS) = 9.33/110 (24, 48, and 72 hours). Maximum irritation score (MIS) = 19.5/110 (1 hour).	Conjunctivitis was noted in all the animals. Opacity resolved within 48 hours post instillation. The conjunctival irritation resolved completely in all animals by the study day 14. **Minimally irritating to eyes**
Primary Dermal Irritation 4-hour exposure 14-day study Irritation scored by method of Draize	Rabbit - New Zealand White (6 ♂) Dose: 0.5 mL (purity not known) of test substance applied to 1" × 1" patch of skin Occlusion for 4 hours.	Primary irritation score (MAS): 6/8.0 (24, 48, and 72 hours). MIS: 6.33/8 (72 hours)	Well defined to severe erythema and slight to moderate edema was observed in all test animals during the study. Skin irritation not resolved in 50% of animals by the end of the study (day 14). Mild to moderate blanching, pinpoint eschar and desquamation were noted in the majority of test animals up to and including the day 14 observation period. **Severely irritating to skin**
Dermal Sensitization Buehler method. 6 hour exposure per application. Irritation graded at 24 and 48 hours after each application.	Guinea pigs - Hartley albino (topical application) *Induction phase* Test group (5/sex): 0.4 mL of 75% diallyl disulfide in water. 3 applications (days 0, 6, and 13). Positive control (3/sex): 0.4 mL of 0.5% DNCB (in acetone/ethanol). 3 applications (days 0, 6, and 13) during induction *Challenge phase* (Day 27) Test group (5/sex): 0.4 mL of 25% diallyl disulfide in distilled water.	Positive	Mild to moderate erythema at 24 hours and mild erythema at 48 hours in majority of test animals when challenged and then verified by the rechallenge. **Skin sensitizer**

Study	Species/Strain and Doses	Results	Target Organ/Significant Effects/ Comments
	Challenge control (5/sex): 0.4 mL of 25% diallyl disulfide in distilled water Positive control DNCB induced group (3/sex) and DNCB control group (2/sex): 0.4 mL of 0.1% DNCB (in acetone/ethanol) and 0.4 mL of 0.2% DNCB (in acetone/ethanol). *Rechallenge phase* (day 34) Test group (5/sex) and rechallenge control (5/sex) 0.4 mL of 25% diallyl disulfide in distilled water *DNCB: 1-chloro-2,4-dinitrobenzene*		
Genotoxicity: Bacterial Reverse Mutation Assay (Ames test)	Bacterial strains TA98, TA100, TA1535, TA1537, and TA1538 of *Salmonella typhimurium* in the absence and presence of metabolic activation. 50,100, 250, 500, 1000 and 3000 µg/plate in the presence of S9 mix and 10, 25, 50, 100, 250 and 1000 in the absence of S9 mix.	Negative results	Diallyl disulfide did not cause a positive increase in the number of histidine revertants per plate of any of the tester strains either in the presence or absence of microsomal enzymes prepared from Aroclor-induced rat liver (S9). **Not mutagenic**
Short term studies (Tier I) DACO 4.3.1, Short-term Oral (90 day rodent) DACO 4.3.2, Short-term Oral (90 day rodent and /or 12 month dog)) DACO 4.3.4, Short term Dermal (90 day rodent)		Data Waiver Request: Rationale: Low exposure (method of application and low use rate). No toxicological concerns from low exposure. Acceptable	
Genotoxicity testing (Tier II) DACO 4.5.7: In vivo cytogenetics		Data Waiver Request: Rationale: Low exposure (method of application and low use rate)	

Study	Species/Strain and Doses	Results	Target Organ/Significant Effects/ Comments
Mammalian Bone Marrow chromosomal Aberration, mammalian Erythrocyte Micronucleus		Not required as the Ames test is negative. In a genotoxicity study, diallyl disulfide has been reported to have clastogenic effect in Chinese hamster ovary cell line by Musk et al. (1997). Because of the metabolism and excretion of diallyl disulfide in vivo, it is unlikely that clastogenic concentrations will be reached in human tissues after exposure. Potential for carcinogenicity is unlikely, based on the in vitro study, because diallyl disulfide induces large number of aberrations at highly cytotoxic doses; without S9 mix. The cells suffering DNA damage are unlikely to survive to develop tumourigenic properties. No concerns from anticipated low exposure. Acceptable	
Developmental toxicity (Tier II) DACO 4.5.3 Prenatal developmental toxicity		Data Waiver Request: Rationale: Low exposure (method of application and low use rate). Not required due to low toxicological concern at Tier I, and anticipated low exposure. Acceptable	
Long term studies (Tier III) DACO 4.4.1, Chronic Oral (rodent and non-rodent) DACO 4.4.2, Carcinogenicity (rodent species 1) DACO 4.4.3, Carcinogenicity (rodent species 2)		Data Waiver Request: Rationale: Low exposure (method of application and low use rate). Not required due to low toxicological concern at Tier I, and anticipated low exposure. Acceptable	
Special studies DACO 4.5.2, Prenatal Development Toxicity (Tier I) DACO 4.5.5, Genotoxicity: In vitro Mammalian Cell Assay (Tier I) DACO 4.5.1, Reproduction and Fertility Effects (Tier III)		Data Waiver Request: Rationale: Low exposure (method of application and low use rate). Not required due to anticipated low exposure. Acceptable	

Table 2 Fate and Behaviour in the Environment

Property	Test substance	Value	Comments	Reference
Abiotic transformation				
Hydrolysis (soil and water)	DADS	Lack of functional groups that hydrolyze	Not expected to be an important route of transformation	HSDB, 2009; PMRA 1736204
Phototransformation (soil and water)	Allyl sulfide	Allyl sulfides do not contain chromophores that absorb at wavelengths > 290 nm	Not susceptible to direct photolysis by sunlight	HSDB, 2009; PMRA 1736204
Phototransformation in air Reactions involving photochemically produced hydroxyl radicals from the atmosphere	Diallyl disulfide	Atmospheric half-life of 11 hours	Non-persistent	HSDB, 2009; PMRA 1736204
Biotransformation				
Biotransformation in aerobic soil and water	Diallyl disulfide	DT_{50} < 4 hours (water)	Non-persistent No transformation products were found.	Arnault et al. (2004; PMRA 1736279); Ramakrishnan et al. (1989; PMRA 1736275)
Mobility				
Adsorption / desorption (soil and sediment) K_{oc} predicted by modeling	Diallyl disulfide	K_{oc} = 270 - 506.7	Low mobility; expected to adsorb to suspended solids and sediment	HSDB, 2009; PMRA 1736204; EPI Suite™; PMRA 1736287
Field studies				
Field dissipation /leaching Study carried out on a US aerobic soil (not characterized): DADS™ was applied using a single row shank at a rate of 10 kg a.i./ha and was applied at a 15 cm depth using a total liquid application of 561 L/ha. Analysis of samples was conducted using purge and trap gas GC-MS	Diallyl disulfide	None available	No residues greater than 5µg/kg (LOQ) found. Non guideline study. No transformation products identified.	PMRA1433434
Aquatic Volatilization DT_{50} predicted by modeling	Diallyl disulfide	DT_{50} = 4 h (river) DT_{50} = 4 d (lake)	Non-persistent	HSDB, 2009; PMRA 1736204

Table 3 Toxic Substance Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		No
Persistence[3]:	Soil	Half-life ≥ 182 days	Half-life < 4 hours
	Water	Half-life ≥ 182 days	Half-life < 4 hours
	Sediment	Half-life ≥ 365 days	Half-life Not available
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life 11 hours
Bioaccumulation[4]	Log K_{OW} ≥ 5		Log K_{OW} 3.56 (estimated)
	BCF ≥ 5000		Not available
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.

1 All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

2 The policy considers a substance "predominantly anthropogenic" if, based on expert judgment, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

3 If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

4 Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log KOW).

References

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2.0 Human and Animal Health

3.0 Environment

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